

1 end-points then one would have to ask.

2 DR. ADAMSON: To in part answer Wayne's
3 question, I think the only way Phase II windows will
4 impact upon the speed of drug development, if we are
5 willing to put into Phase II windows drugs where we
6 have no activity data or the classic Phase II activity
7 data is inactive. Now the past decade we have been
8 unwilling to do that.

9 But just doing Phase II windows, where we
10 have activity data, all it is doing, in my opinion, is
11 delaying the decision whether to move into Phase III.
12 It is not impacting our decision to move into Phase
13 III.

14 Which circumstances can you put an
15 inactive agent in classic Phase II in upfront, and
16 where you have no data into upfront, I think carries
17 still the same ethical considerations, but as far as
18 speeding drug development process, until we are
19 willing to do that, I don't think the Phase II windows
20 are going to speed the drug development process.

21 CHAIRMAN SANTANA: Peter, I will take note
22 to your comment that it has delayed. How has it

1 delayed the process?

2 DR. ADAMSON: Perhaps I will temper that.

3 (Laughter.)

4 VPI fos we knew was active. Or let me
5 take perhaps a more recent example. Topo cyclo we
6 know is active, and we know we have to do a Phase III
7 study of it to determine if it is going to impact.
8 Waiting for Phase II window data -- and I think the
9 reality is we probably didn't wait; we only have so
10 many opportunities to do Phase III. So I perhaps
11 should restate it and say, I don't think it has
12 accelerated our ability to do Phase III trials. In
13 many cases the reality is we only can do so many Phase
14 III trials in pediatric oncology and what to do in the
15 interim.

16 CHAIRMAN SANTANA: Yes, I agree with you;
17 I don't think, based on the data that we have so far,
18 that we could definitely say that it has accelerated
19 the process, but I think we have to recognize that it
20 also has not negatively impacted on it.

21 Okay, Malcom?

22 DR. SMITH: I have several points. Chuck

1 Coltman's question was, has it affected outcome? That
2 is an easy question to ask, but a very hard question
3 to answer because every Phase II window is different.
4 If you amalgamate four or five or ten different
5 trials, there may be no difference, but one trial
6 there could have been a difference in outcome. So it
7 is a very hard question to answer, and they are small
8 numbers, small differences that may or may not be
9 significant, just because we don't have the numbers.
10 So it is quite hard to answer that question with any
11 confidence. We can't say they do or they don't.

12 The other point that you brought up is the
13 question of parameters such as disease progression,
14 and that is one thing that we can say with some
15 confidence, is that disease progression is more likely
16 in the single-agent Phase II window setting than it is
17 when therapy has begun with conventional multi-agent
18 therapy that we know is able to induce remissions or
19 responses in neuroblastoma or Ewing sarcoma or
20 osteosarcoma. So that's come from several different
21 trials.

22 A third point, and one that I thank Steve

1 for circulating our commentary on the Phase II
2 windows, but a point we made in that was that at first
3 relapse many of these issues are the ethical concerns
4 are reduced. The effectiveness of salvage therapy is
5 diminished compared to the effectiveness of upfront
6 therapy. Parents know about cancer treatment and are
7 better able to assess whether they want to
8 participate.

9 And Eric's point, these are tumors that
10 have come back in spite of our known effective
11 therapies, and presumably they are enriched for the
12 clones that we most want to kill and we most want to
13 identify active agents.

14 So I think in terms of looking to the
15 future, and perhaps accelerating pediatric drug
16 development, making better use of that, the first
17 relapse, and looking at some of the new agents in that
18 setting, potentially in a Phase II window setting,
19 before proceeding to a more conventional salvage
20 therapy has a number of advantages.

21 CHAIRMAN SANTANA: I will take one more
22 question because I want to make sure we stay on time.

1 So we will let Dr. Cohn comment.

2 DR. COHN: Thank you. I just wanted to
3 make one comment about the biologicals, and that is
4 many of them I don't think would, even if we are
5 ending up now deciding the Phase II upfront windows
6 would not be a good thing to do, I think Pat's study,
7 where he used retinoic acid, demonstrated very nicely
8 that many of these biological agents work best in a
9 setting of minimal residual disease. So to use them
10 upfront, when you've got disease from head to toe,
11 probably isn't the best way to approach some of these
12 biologic agents anyway.

13 CHAIRMAN SANTANA: Susan, one last comment
14 or question?

15 DR. WEINER: Yes, I had the dubious
16 privilege of being involved in that consensus panel,
17 as you describe it, a number of years ago. It comes
18 as no surprise that the parents at St. Jude, with the
19 kind of consent form that we had recommended, are not
20 agreeing to participate in window trials for new
21 patients, for newly-diagnosed patients. The parents'
22 perspective is really give it the best shot you've

1 got, and a Phase II window trial is not exactly
2 equivalent to that.

3 My question also extends to Drs. Smith and
4 Hirschfeld, and that is that it was my understanding
5 from this panel that this represented a set of
6 guidelines by which to judge and decide on Phase II
7 window trials in general. I wonder, what is the
8 relationship was between these document and our
9 discussion today and what guidance the FDA may take
10 from that?

11 DR. HIRSCHFELD: We, I think, will defer
12 that until after the break, when we have a very
13 specific question which I think Dr. Santana will pose
14 to the panel to help frame a response.

15 CHAIRMAN SANTANA: Well, with that, we
16 will take a 10 -- Malcom, do you want to comment?

17 DR. SMITH: Well, just to address Susan's
18 question in terms of, that guidance has really guided
19 CTAP's review of Phase II window studies, and
20 specifically in terms of the informed consents now do
21 contain all of those things, and really the number of
22 Phase II studies that have been initiated, single-

1 agent Phase II window studies has been small, quite
2 limited, since the meeting. There have been some.
3 They have conformed to the guidelines from the Phase
4 II window meeting.

5 CHAIRMAN SANTANA: Yes, and at St. Jude,
6 where we initiated some of these Phase II window trial
7 concepts, I think we have been very, very attuned to
8 following the guideline as much as possible. I think
9 it reflects what you mention in terms of where we are
10 with the informed consent process for these studies.

11 With that, I want to take a 10-minute
12 break and resume half after the hour, so people can
13 relieve themselves, and then we will get started and
14 do the questions.

15 (Whereupon, the foregoing matter went off
16 the record at 3:18 p.m. and went back on the record at
17 3:32 p.m.)

18 CHAIRMAN SANTANA: Okay, let's go ahead
19 and get started, so we can finally get to some advice
20 to the FDA on the questions that they have posed.
21 They have posed four questions for us.

22 For the public record, what I will do is

1 I will read the brief introduction to the question,
2 pose the question, and then we have asked Dr. Adamson
3 and Dr. Rackoff to comment. The way we will do it is
4 Dr. Adamson is going to take each one of the questions
5 and give his perspective. We will have a public
6 discussion about the question. We will move on to
7 two, to three, to four, and then Dr. Rackoff will come
8 at the end and give us an overview and his comments.
9 Okay?

10 So the first item is the paragraph that's
11 introductory to the questions that relates that, "The
12 common approach for selecting starting dose for Phase
13 I studies in children with cancer in cytotoxics is to
14 begin at 80 percent of the adult maximally-tolerated
15 dose, the MTD.

16 "Children who currently enter Phase I
17 studies tend to be more heavily pre-treated with other
18 therapies than historically had occurred. In
19 addition, many newer therapies are not cytotoxic in
20 the manner that previously-developed therapies were or
21 may have different modes of action, including
22 modulation of cellular-signaling pathways."

1 So the first question is: "If a potential
2 therapy has an established dose in adults based on the
3 optimal biologically-effective dose, the OBD, what
4 principles should be applied to designing studies in
5 children? For example, should the starting dose be a
6 percentage of the adult dose, as historically has been
7 done? Should the same exposure or AUC be targeted?
8 And what role should pre-clinical data play in these
9 kinds of study designs?"

10 Peter?

11 DR. ADAMSON: I will preface this by
12 saying I tried to take the questions that Steve had
13 originally posed and foresee what some of the comments
14 might be. As you will see from these slides, I have
15 been more successful on certain occasions and less on
16 others. But it, I think, will serve as a bridging
17 point for discussion.

18 So here are my way of restating the first
19 questions. The first one that we are going to talk
20 about is the Phase I design issues, optimal biologic
21 dose, and then we will get to the following three. I
22 will sum up and then turn it over to Wayne, talking

1 about the importance that we face in prioritizing
2 agents, and then ultimately when should the rule be
3 invoked.

4 So the first question, Phase I design,
5 when one has the optimum biologic dose, how is this
6 going to impact pediatric Phase I design? I think the
7 challenge that we are going to face, if we try to
8 implement this, is one of tissue acquisition. Frank
9 Balis had commented on this earlier.

10 Essentially, the procedure must be minimal
11 risk to be acceptable. So for leukemia studies,
12 getting the leukemic blasts I think was going to be
13 pretty straightforward; tumors invading the bone
14 marrow, again, pretty straightforward. When we start
15 moving beyond that for soft tissue tumors, immediately
16 we are going to get into a more difficult area in
17 order to obtain tissue. Ultimately, we will still be
18 left with a question, as Eric posed, of: Are we
19 really measuring the correct end-point? Not only is
20 it important to know, are we measuring the correct
21 end-point, but what is the specificity of the drug?

22 We have learned more often than not that

1 a drug we think is working in one way turns out to
2 have worked in additional ways. So the mere fact that
3 we are measuring one end-point, it may not be the most
4 meaningful end-point to explain the biologic effect of
5 the drug. In many respects, the fluorouracil
6 inhibitors are a good example of that, where they have
7 activity beyond mutated RAS.

8 I foresee that we are going to be using
9 pharmacologic data as a surrogate more often than not,
10 and in this case the AUC. The advantage of this is
11 that by targeting exposure, it is really independent
12 of what the specificity of the drug is for the target.
13 In some respects it may be independent of what the
14 mechanism of action is. If we have an exposure that
15 is correlated with an effect, the challenges become
16 and the dangers become, we don't always or we rarely
17 know what the correlation between the plasma
18 concentrations that we measure is with the target
19 tissue exposure. Ultimately, we assume that there is
20 some correlation, and it remains undefined. The hope,
21 in fact, is that AUC turns out to be a good surrogate
22 for tissue exposure.

1 How might this impact starting dose? I
2 think even if we were fortunate enough to have data on
3 what the optimum biologic dose truly was in adults, it
4 may differ between adult and pediatric tumors. So the
5 optimum biologic dose may not be the same in a
6 pediatric tumor as in an adult tumor. Ultimately,
7 what this means is we are going to need pre-clinical
8 data at least to give us a relative comparison of what
9 an optimum biologic concentration may be. If not an
10 absolute, we may be able, if we use similar models, to
11 say, for this tumor, we are going to need twice the
12 exposure that we do for an adult tumor. Absolute
13 exposures probably carry more dangers with them, but
14 relative exposures may be a reasonable way to go.

15 Again, to emphasize that chances are the
16 optimum biologic dose may not be known following adult
17 Phase I or Phase II trials. Right now we are faced
18 with, well, how long do we wait to have this data? If
19 we truly wait until the adults are confident they have
20 defined an optimum biologic dose, we are simply going
21 to increase the lag time to initiate pediatric
22 clinical trials.

1 So I think, although we need to look to
2 the future, to a time when we can rapidly define an
3 optimum biologic dose, over the upcoming years it may
4 be premature to think that we are going to be able to
5 do this. To delay pediatric trials excessively in an
6 effort to define this in adults, I think is going to
7 be doing children a disservice and is going to be
8 setting pediatric drug development back further.

9 Finally, to come to pharmacology, and here
10 I just want to build on what Mary and Clint and Steve
11 have presented, but I want to take this emphasis:
12 Phenotype matters. There is no question that
13 pharmacogenomics, pharmacogenetics are critical pieces
14 of information, but in fact, as Mary pointed out,
15 genotyping is simply going to get easier.

16 What is not easy is defining phenotypes.
17 In this case, phenotype, Clinton very nicely displayed
18 some of the strategies where we can obtain phenotyping
19 data with limited sampling methods, and I think we are
20 going to have to look to do that more frequently.

21 Certainly, in Phase I trials we routinely
22 define phenotype, and I think Mary gave compelling

1 reasons why we must start looking at obtaining
2 genotype, because this is going to be the one clear
3 situation where we are going to have both phenotype
4 and genotype data available.

5 More importantly, I think, the Phase I
6 pharmacokinetic/pharmacodynamic data that we generate
7 will set the stage for Phase II and III clinical
8 investigations, and I think there is going to be an
9 ongoing need to obtain genotyping data and then
10 phenotyping likely through limited sampling methods,
11 not only in Phase I, but in Phase II and III.

12 So that's my few cents on question one,
13 and maybe I will turn it back to Victor then.

14 CHAIRMAN SANTANA: Okay, further comments
15 and discussion on question one? Dr. Bernstein?

16 DR. BERNSTEIN: I would just like to
17 support Peter's point that really we don't want to
18 wait until an optimum biologic dose has been defined
19 in adults in order to initiate pediatric trials. We
20 really want to get in sooner, and, in fact, as Eric
21 was explaining before or suggesting before, that
22 perhaps the place for us to get in is as early as the

1 dose level at which Grade 2 toxicities are being seen
2 in adults, because at that point we know that there is
3 at least a dose that has biological activity, and
4 maybe we can think about initiating pediatric trials
5 at that point, without even waiting for completion of
6 the adult Phase I trial, and build into our study
7 designs the fact that, if the adults are able to
8 escalate very rapidly, that we can then skip a few
9 dose levels in order to catch up, so that we don't
10 have to duplicate things that have already been done.

11 So I would just like to suggest that what
12 we want to do is work on study designs that enable us
13 to get trials going sooner, to get trials completed in
14 a reasonably short time, rather than waiting for as
15 much information as we would need in order to define
16 what is truly a biologically-active dose.

17 CHAIRMAN SANTANA: Clinton?

18 DR. STEWART: Peter, I heard you describe
19 the optimal biological dose, and earlier I guess it
20 was Ed talked about the biologically-effective dose.
21 Frank talked about a minimally-effective
22 concentration. Peter, you talked about measuring AUC.

1 We've got all these parameters floating around.

2 It seems like, I don't know, maybe that
3 reflects sort of the confusion in the system. It
4 seems to me if we were to pick -- this whole
5 dependence on dose is a little bit concerning to me,
6 and it goes back to the slide that I showed during my
7 talk about the study that we did, the POG 92-75 study,
8 where you escalate dose, but you are not escalating
9 exposure. So you can change the dose until the cows
10 come home, but you are not changing the exposure that
11 the child is getting.

12 So I think we've got to be careful about
13 this dependence upon changing dose and thinking that
14 you are changing what kind of exposure that the child
15 is getting. So I like the idea of the AUC or the
16 minimum effective concentration that Frank talked
17 about, but if we are going to do that, then we are
18 going to have make the commitment of resources and the
19 infrastructure to be able to follow through with that.
20 It also means that I don't think we can do that with
21 every agent that comes down the pike. I think we are
22 going to have to be selective about that, because it

1 does require a great deal of work and commitment of
2 resources to be able to follow through with that. So
3 that's a comment.

4 The question I would ask you, Peter, this
5 is a slightly different one, but you were talking
6 about genotyping in Phase II and Phase III studies.
7 Assuming that a patient is a genotyped in a Phase I
8 study, you wouldn't genotype them again, would you?

9 DR. ADAMSON: No.

10 DR. STEWART: You are not talking about
11 rephenotyping or regenotyping?

12 DR. ADAMSON: No.

13 DR. STEWART: Okay, I just wanted to make
14 sure about that.

15 CHAIRMAN SANTANA: But let me follow up on
16 Clinton's comment. I think the advice that I would
17 propose, and certainly this is my opinion and
18 certainly not that of the Committee, is that you have
19 different scenarios. You have a scenario where there
20 is a classical way of doing Phase I studies, where you
21 start at some level that has either been predefined
22 based on adult data or concomitantly as the adult data

1 and the pediatric study are being done.

2 I think that will apply and has worked
3 very well for the majority of the things that we have
4 done with cytotoxics. Continuing with the cytotoxic
5 story, but there may be certain drugs, which Clinton
6 was referring to, in which we may have pre-clinical
7 data that supports that a different concept be applied
8 to defining the escalations or how the Phase I study
9 is done. I can't give you a broad recommendation on
10 that. It is going to depend on what pre-clinical data
11 exists, either from relevant pediatric models or other
12 models that may exist that would then indicate that
13 maybe a different end-point, like the AUC or the
14 systemic exposure, may be more relevant in applying
15 your design to the Phase I concept.

16 So I think for cytotoxics we want to move
17 to No. 2, but we have to recognize that there is not
18 a lot of infrastructure to support that at present,
19 and that we have to be very selective in which drugs
20 we could apply that principle to. Although ideally it
21 should be with every drug, I don't think realistically
22 we are at that point yet.

1 For biologics, I think it is a completely
2 different story, in my view. I think the principles
3 of the traditional Phase I escalation I think may not,
4 as you heard earlier today, may not apply. I think in
5 those settings I would argue more like Frank was
6 saying earlier, that in those settings with biologics,
7 not cytotoxics, that we do the parallel scenario
8 studies, because, clearly, the differences in activity
9 or potential toxicity may be very different in the
10 populations.

11 DR. HIRSCHFELD: May I just ask for a
12 little clarification? I thought I was hearing that it
13 might be appropriate in the Phase I study to look at,
14 as an end-point, the first doses which you see Grade
15 2 toxicity, independent of whether there is a target
16 or some other biological assay, but that your Phase I
17 study would guide you toward a toxicity, and that, in
18 turn, would be informative.

19 CHAIRMAN SANTANA: Do you want to address
20 that? I think you were the one --

21 DR. ADAMSON: I didn't raise it, but, Ed,
22 if you want, I think the intent is, when you see a

1 Grade 2 in adults, is that a reasonable time to say,
2 okay, this is a reasonable dose to start in children,
3 and then we can catch up to wherever the adults are
4 when they have gotten to their MTD or closer to the
5 MTD? At least that was my interpretation.

6 DR. KORN: Yes, I just want to add, I
7 mean, I didn't say it, but it should be understood, of
8 course, that if you are using a molecular target or
9 some targeted response, that if you see toxicity, you
10 have to stop escalating and back off.

11 DR. HIRSCHFELD: Thank you for that
12 clarification. Just so that we understand, a
13 potential direction for Phase I, an adult study would
14 have as one of its end-points some toxicity,
15 independent of whether a targeted dose or some
16 bioassay was going to be invoked, and that that
17 toxicity, in turn, could be a guide for initiating
18 pediatric studies.

19 CHAIRMAN SANTANA: Malcom?

20 DR. SMITH: Two comments: One is that, in
21 terms of the AUC and that as an end-point, you know,
22 we have done that with 06-benzyl bromine, and so

1 there's precedence for doing that, and I agree
2 completely with Peter that I think we will be doing
3 that more and more in the future as we have a systemic
4 exposure that has the appropriate effect in adult
5 patients, and then we want to make sure that, when we
6 use a similar dose in children, that we are attaining
7 that systemic exposure. So we have done that, and I
8 think, as Peter says, we will be doing that more in
9 the future.

10 The second comment is I would caution, we
11 can do what Steve just asked and what Ed said; we can
12 start at the first Grade 2 toxicity. I would caution
13 our goal isn't to start pediatric studies as quickly
14 as we can. Our goal is to complete them as quickly as
15 we can. If we add five or ten patients below the MTD,
16 using that design, whereas using another design we add
17 all of the patients closer to the MTD, and that takes
18 your patients, then, in fact, we are studying more
19 drugs; we're completing perhaps more studies more
20 quickly, and the point I made earlier: that because
21 adult Phase I trials can be completed so quickly with
22 dose levels occurring very quickly, the rate-limiting

1 step with the design that Ed described is most
2 commonly getting to the adult MTD, so that you can
3 jump over three or four levels in the pediatric study
4 to get to that.

5 So I think we need to keep our eyes on the
6 prize, and in terms of Phase I that is the number of
7 drugs that we can study, hopefully, picking the very
8 best ones that we can.

9 DR. ADAMSON: Yes, I agree, Malcom, to an
10 extent. Part of the problem, at least over the past
11 few years, has been that we haven't had enough drugs
12 to study for children, and that we have had children
13 who simply have not gone on to study because there
14 were no open studies.

15 So it is always a balance as far as -- it
16 is not only completing studies on time, but it is
17 making studies available in a timely fashion. I don't
18 think there is a hard-and-fast rule as far as when to
19 start. Clearly, for some of these, we have started,
20 in my opinion, much too late, and that is when the
21 drugs have been on the market.

22 But there will have to be a balance to

1 when we think it is appropriate, and certainly, if all
2 patients are going on to open studies where the adult
3 MTD is known, then there will be less pressure to open
4 studies earlier.

5 DR. PRZEPIORKA: During lunchtime I was
6 encouraged to re-ask two questions that were deferred
7 from this morning, one of which had to do with the
8 dose when moving from an adult to a pediatric study,
9 and whether or not you should continue on a milligram-
10 per-kilogram dosing versus milligram-per-meter-
11 squared, especially in light of the fact that we
12 recently have a drug that went out with a milligram
13 dosing in adults without any basis on weight
14 whatsoever? So no one is sure how to do this in
15 children.

16 Secondly, just to readdress the question
17 of what is clinical and what is research, and we have
18 now the option for participants not to participate in
19 the pharmacokinetic studies. How many patients do you
20 really want to get pharmacokinetic studies in this
21 heterogeneous pediatric population before you're
22 certain that you really have the dose to get the right

1 AUC?

2 CHAIRMAN SANTANA: Clinton?

3 DR. STEWART: Well, I would actually like
4 to address the second question first, and that would
5 leave Steve with the first question, which is the more
6 difficult one.

7 The issue of clinical versus research, as
8 far as it goes with pharmacokinetic studies, I think
9 is a very important one and actually one we talked
10 about at lunch today. A Phase I study, let's talk
11 about that specifically first. Whether it is part of
12 the primary objective or part of a secondary objective
13 is one way that we look at it at St. Jude, whether or
14 not is considered in the informed consent aspect, is
15 whether or not a child is to be -- to participate in
16 the study, to receive the study drug, that they have
17 to participate with the pharmacokinetic studies. If
18 it is a secondary objective, it is part of a checkbox
19 and they are allowed not to participate. I guess that
20 is just one comment.

21 CHAIRMAN SANTANA: Could I follow up on
22 that, Clinton?

1 DR. STEWART: Yes.

2 CHAIRMAN SANTANA: I think the point is
3 that if the end-point is that you are going to define
4 the toxicity based on a pharmacokinetic parameter, you
5 can only realize that end-point if you get PK;
6 whereas, if PK is a secondary issue to the design,
7 that the main design is a completely different
8 question, then I think in those circumstances then the
9 option of yes or no PK is something that you can
10 allow.

11 DR. STEWART: Right.

12 CHAIRMAN SANTANA: But in the first
13 scenario, if you are really trying to define the
14 toxicity based on AUC, how can you not get PK? In
15 that scenario it is absolutely crucial to that study.
16 So you either participate in the study or you don't.

17 DR. STEWART: Right. So then the second
18 part of your question is, how many patients do you
19 need? And that is something that I have been
20 listening to as we talk about the number of patients
21 in a Phase I study. I mean, obviously, one of the
22 things you want to do is to minimize the number of

1 patients that receive what is considered -- and I
2 hesitate to use this term, but a subtherapeutic dose
3 and maximize the opportunity that a child would have
4 for a therapeutic response.

5 So you want to try to minimize the numbers
6 of patients in a Phase I study, I would assume, and
7 yet I counterbalance that with the need to learn about
8 the disposition of a drug in the pediatric population.
9 One of the references that Steve sent out was the
10 paper from Elizabeth Eisenhower, who was an author on
11 it out of JCO. It was a consensus conference about
12 Phase I studies. My colleague, Mark Ritane, wrote in
13 that about the need for studying additional patients,
14 and one of the ways he suggested doing it was to study
15 more patients at the MTD. So you had 20 to 30
16 patients -- this is in the adult population -- 20 to
17 30 patients at the MTD.

18 Now Dr. Boyett is over there squirming in
19 his seat because, you know, there is no way to say
20 that is going to provide a, quote/unquote,
21 "statistically-valid" estimate of clearance in that
22 particular populations, but what it will do is it will

1 give us a better handle on the estimates of clearance
2 than studying two or three children at a particular
3 dose.

4 So how many children do you need? I can't
5 give you that number, but I can tell you we do need to
6 study an adequate number of children, more than, say,
7 six or eight or ten. I would be an advocate of being
8 sure that in our Phase I studies we don't sacrifice
9 the knowledge that we need to gain from those
10 pharmacokinetic studies that we can use as we move
11 into the Phase II, that we just don't sacrifice that
12 knowledge.

13 CHAIRMAN SANTANA: Dr. Bernstein?

14 DR. BERNSTEIN: I won't disagree with
15 Clinton about the pharmacokinetics, but I would only
16 disagree with the setting and say that what we can
17 start to do more of is, as we take drugs into Phase
18 II, especially if there is a limited sampling strategy
19 that has been designed, is that we can look at the
20 pharmacokinetics in the initial Phase II population as
21 well to complete the number that is required to
22 actually get an idea of the things like Clinton is

1 talking about.

2 CHAIRMAN SANTANA: Have we satisfied this
3 question, Dr. Hirschfeld?

4 DR. HIRSCHFELD: I think Dr. Leeder was
5 going to make a comment --

6 CHAIRMAN SANTANA: Oh, I'm sorry.

7 DR. HIRSCHFELD: -- about dosing, yes.

8 DR. LEEDER: Well, these discussions have
9 been recorded for all posterity, and I really don't
10 want to go down on record as the individual who sets
11 policy for converting adult doses to pediatric doses.
12 But there are a couple of points worth making.

13 One point is that, until November the
14 19th, which is when I got the email message from Steve
15 that kind of laid out what might be expected of me,
16 and this is specifically this issue of converting
17 adult doses to pediatric doses, I had not really
18 seriously considered this whole aspect of the
19 ramifications of correcting clearance for body weight
20 versus body surface area versus liver mass, or
21 whatever it is.

22 It is my impression only, without having

1 a detailed slog through the literature, that the
2 apparent differences in clearance between adults and
3 pre-pubertal children tend to be less when corrected
4 for body surface area than for kilogram body weight.
5 Now I don't want to completely cop out on an answer,
6 and what I am going to suggest is that perhaps some of
7 the information is available to us, and some of the
8 notes that I made have been to go back and look at
9 some of the existing pediatric data for compounds such
10 as medazalam, carbomezapine, which are pretty well
11 accepted to be measures of P450A4 activity, for
12 example, where there are a lot of pharmacokinetic data
13 in children.

14 I think one thing that needs to be borne
15 in mind is that pharmacokinetics classically have
16 described the disappearance of the parent compound.
17 In cases like Irinotecan, where it is an active
18 metabolite, what is important is probably the exposure
19 to the parent compound. And the point I am trying to
20 get at is the fact that perhaps the pediatric clinical
21 oncology arena maybe ought to take advantage of some
22 of the information that is available for some

1 compounds in the pre-clinical testing phases with
2 respect to in vitro drug metabolism.

3 Certainly for a lot of compounds there is
4 a process that is called reaction phenotyping, where
5 a battery of human liver microsomes that have been
6 phenotyped for particular activities, recombinant
7 heterologously expressed human enzymes, are used to
8 map the drug metabolism pathways that are involved in
9 the disappearance of the parent compound, and perhaps
10 the formation of the pharmacologically-active anti-
11 neoplastic compound, with the intent of at least
12 identifying polymorphic pathways or perhaps some would
13 say avoiding them. Maybe you don't want a compound
14 that is a substrate for 2D6 which is deficient in 5 to
15 1 percent of the Caucasian population.

16 The other reason this process is completed
17 is to characterize and perhaps minimize drug-drug
18 interactions. The point I am trying to make is that,
19 if we go back through the literature and look at this
20 issue of clearance with respect to the metabolic
21 pathways, the specific metabolic pathways that are
22 involved, how those metabolic pathways change during

1 development, whether or not they are better correlated
2 to thing such as a correction for body weight, body
3 surface area, or liver mass, that it may be possible
4 for specific compounds to put all this information
5 together and come up with some sort of a rational
6 conversion factor.

7 But, as a starting point, again, I would
8 like to repeat that my impression is that the
9 differences are probably least or less with body
10 surface area than with kilogram or total body mass,
11 and I think it is just a little bit premature to
12 pursue the liver mass at this point in time, until we
13 do a few more studies.

14 CHAIRMAN SANTANA: But how do we address
15 the issue that Donna was trying to, I think, hint at,
16 which is, we have a product or an agent that's been
17 approved on a milligram basis? How do we really
18 relate that in terms of the type of studies and where
19 we start in pediatrics? Because to me that's an
20 issue. Can you shed some light on that? Because I
21 think we are going to be seeing that more and more
22 with some of these biologics. It is not going to be

1 milligram per kilo, milligram-per-square-meter. It is
2 going to be some total dose.

3 DR. LEEDER: I find, and maybe Clinton can
4 comment on this as well, I find it very difficult,
5 just from the concept of dumping a specific mass of
6 drug into a volume of varying ranges, to be able to
7 predict what concentration is going to come out. So
8 I would probably pick any correction over a straight
9 milligram dose.

10 (Laughter.)

11 CHAIRMAN SANTANA: Clinton?

12 DR. STEWART: So, as you probably know, we
13 are faced with that with one of the upcoming clinical
14 trials that we are going to have. One of the things
15 that I have proposed, and Peter and I have talked
16 about this, is then the first three to five patients,
17 what we will do is we've got the dose; the dose was
18 decided in adults in milligrams. We have converted it
19 using a 1.73-meter-squared typical adult to a meter-
20 squared, milligram-per-meter-squared dose in children.
21 So what we will do is we've got the assay up online,
22 and the first three to five patients we'll measure the

1 concentrations and we will see what the levels are in
2 our children relative to what they were in the adults,
3 and we will be prepared to go from there.

4 So, I mean, that doesn't help the first
5 child that is enrolled in the study very much, but
6 that is how we are going to be prepared to react to
7 that situation. So, I mean, that is one thing I can
8 offer up.

9 One other thing I would like to say in
10 terms of our experience with Topotecan, and I tried to
11 allude to it a little bit earlier with the infants,
12 the children less than two, it does appear that, if
13 one were to normalize the clearance for body weight
14 per kilogram, it does seem to normalize the
15 differences between the infants and the older
16 children.

17 So what I am saying there is I think that
18 we have to be very careful when we talk about
19 children. All children are not the same. You've got
20 the little children, and then you've got the bigger
21 children. I think that, as Steve pointed out, there
22 are maturational differences in the way that they

1 eliminate drugs. So we've got to be careful about
2 just making the straight -- I mean, it is a difficult
3 conversion from adults to children, but then even
4 within the children, quote/unquote, "children"
5 population, we've got infants and then those kinds of
6 considerations. So I hate to make things even more
7 complex, but we have to consider that.

8 CHAIRMAN SANTANA: Steve?

9 DR. LEEDER: If I could make one comment
10 that might help simplify things, again, it goes back
11 to this point that the closer the children -- for
12 example, adolescence, post-puberty, chances are when
13 you look at -- let me back up a bit and say maybe we
14 can get some insights, for example, from the shapes of
15 growth curves -- we all have access to the growth
16 charts -- and look at when the growth charts start to
17 flatten out as being the points where there are fewer
18 changes with age.

19 So one of the areas where the growth
20 charts flatten out is after puberty. So perhaps it
21 might be possible to go directly from an adult dose,
22 using an adult dose on -- correcting for whatever

1 index you wish -- in a post-pubertal individual.

2 Before that point, it gets a little bit
3 more difficult. Certainly the most difficult region
4 would probably be the first year of life, I think
5 where it is such a dynamic process that I would hate
6 to predict what the appropriate scale ought to be in
7 converting an adult dose to an effective but not
8 toxic, or an optimum, dose in that age range.

9 CHAIRMAN SANTANA: Pat?

10 DR. REYNOLDS: I think one of the things
11 we haven't considered in this is that you have very
12 young children. You can't often take the formulations
13 that are developed for adults. We certainly see this
14 with the oral retinoids as being problem.

15 So the bioavailability of these agents, if
16 you are dumping it out of the capsule and trying to
17 mix it in with applesauce, or whatever it is, is going
18 to change. So that is another parameter that needs to
19 be considered in this. You can't necessarily directly
20 translate these formulations, and some formulation
21 development may be necessary.

22 CHAIRMAN SANTANA: Okay, I think we have

1 pretty much covered this, Dr. Hirschfeld, unless you
2 wish for us to make any comments?

3 DR. HIRSCHFELD: I thank you for all the
4 input.

5 Did you have something you wanted to add,
6 Dr. Rackoff?

7 DR. RACKOFF: Pat made the point I was
8 going to bring up.

9 DR. HIRSCHFELD: Okay, excellent. Okay,
10 let's move on then.

11 CHAIRMAN SANTANA: Yes. So the second
12 question has to do with, and I will read the question,
13 but it has to do with issues of extrapolation and then
14 what efficacy data would be necessary for product
15 labeling for pediatric indications. So the question
16 reads, for the record:

17 "If tumors that are considered to
18 represent the same disease or condition are found in
19 two different populations and/or share a common
20 biological mechanism that is supported by a body of
21 scientific evidence that is generally accepted, and a
22 therapy targets that mechanism, what type of studies

1 would validate extrapolation of efficacy findings from
2 one population to the other?" So this is the question
3 of extrapolation of data.

4 Then the second part to the question is:
5 "Product labeling to support a marketing claim usually
6 is dependent upon demonstration of a patient benefit
7 and an assessment that it is safe and effective for
8 the intended use. If activity is noted in adults, and
9 the same tumor type, based on generally-accepted
10 criteria, such as histology, cytogenetics, common
11 biological mechanisms, et cetera, exist in children,
12 what evidence would be needed to establish efficacy
13 for product labeling; that is, to make a market claim
14 for children with cancer?"

15 Peter?

16 DR. ADAMSON: I have very little to put
17 forth, but I will throw out a suggestion. I think
18 efficacy extrapolations are going to only apply in
19 limited situations, for all the reasons you have
20 simply stated in that question, where biology, and so
21 forth, is the same between adults and children.

22 However, we all can name situations where

1 that occurs. In my opinion, we are still going to
2 need Phase I, and likely some Phase II data, in
3 pediatric patients. However, if the pediatric Phase
4 II data is consistent with the adult Phase II data, I
5 would argue that that ought to be sufficient to extend
6 labeling, if the adult randomized trial has shown
7 efficacy, and that we need not attempt to repeat, nor
8 would we likely have the ability to repeat, a Phase
9 III randomized trial in children.

10 My only other comment along these lines
11 comes back to, Steve, one of your opening comments
12 about when the rule would be invoked. If I understood
13 correctly, you said for certain diseases, an automatic
14 waiver would be granted: prostate cancer, breast,
15 lung. I would argue that granting an automatic waiver
16 for that would be detrimental to pediatric patients.

17 The reason I say that is that one can
18 envision that there is a new agent, a signal
19 transduction inhibitor that's highly effective in
20 prostate, and that signal transduction pathway we
21 learn is a relevant pathway for pediatric tumor. If
22 a waiver is granted, then we will be doomed in that

1 situation.

2 So maybe I will leave it there and let the
3 discussion follow.

4 DR. HIRSCHFELD: Well, Peter, first, I
5 want to thank you for the advice, and I think the
6 advice you propose there is at least consistent with
7 our thinking on the question.

8 In terms of, we'll take the prostate
9 cancer paradigm. If one is defining the indication,
10 and this would represent a paradigm shift, if one
11 defines the indication as, we'll say, a certain
12 Gleason stage prostate cancer or hormone refractory
13 prostate cancer, that's one circumstance. But if one
14 is defining the indication as tumors that are
15 dependent on a certain signaling pathway and have
16 other characteristics, then the Pediatric Rule could
17 be invoked.

18 When the rule was first developed, we
19 didn't have, or didn't anticipate, the tools to make
20 these, what could be called, cross-histologic
21 diagnoses or mechanistic-based. But our thinking has
22 evolved as the science has advanced, and what we would

1 need would be a very firm scientific basis to make
2 that extension, but if there was a firm scientific
3 basis to make that extension, then in that case I
4 think the rule could be triggered.

5 I would like to ask Dr. Pazdur if he would
6 add some comments?

7 DR. PAZDUR: What you want and what we may
8 want has to be supported by the law, because basically
9 this is a mandate. Okay? So it is not an optional
10 thing or it's not like, "Would you please study this
11 perhaps?" It is a requirement that the companies
12 study this, study the indication.

13 So, as Steve mentioned, it would have to
14 be kind of a paradigm, kind of sea change, where the
15 academic community, treating oncologists in general,
16 and a general scientific acceptance would be that
17 these are the same diseases or entities that would
18 represent identical populations with the same disease.

19 It couldn't be just that we're studying a
20 drug that has overexpression or targets topoisomerase
21 1 and, therefore, we are going to then make the
22 company study all tumors that have overexpression of

1 topoisomerase 1, do studies in pediatric tumors, so
2 express that.

3 So it is really a level, since this is a
4 requirement and a mandate, that has a legal
5 implication that we would have to be very careful in
6 applying and would have to have a scientific
7 foundation that is well-accepted by the community.

8 CHAIRMAN SANTANA: Just as a followup of
9 that in terms of my own perspective is I think in
10 terms of these issues of two populations and what data
11 can be extrapolated from one or another, and although
12 the question is posed as an efficacy question, I would
13 caution that safety also has to be a part of the
14 equation. So when one tries to extrapolate data from
15 one population to the other, one has to look at
16 certain parameters that may indicate a different
17 scenario of safety may be similar to some of the PK
18 discussions we've had earlier today.

19 So it is just not a matter of saying the
20 populations are very similar in terms of the diseases,
21 in terms of the biology, and therefore, the efficacy
22 should be the same, but there may be some minor

1 differences in safety that also should be a part of
2 the equation.

3 DR. HIRSCHFELD: I appreciate that
4 comment, Dr. Santana, and that is a major concern not
5 just in oncology, but across all of pediatric
6 therapeutic development in terms of, how do we know
7 that we are getting adequate safety data, that
8 something could be labeled?

9 Just, Peter, one other point: We have
10 another program, an incentive program, for those
11 circumstances where we would like to encourage
12 development in pediatrics but we can't invoke a
13 mandate. That program has been spectacularly
14 successful in general. In oncology we have found that
15 companies are now learning about it and have not been
16 shy about making proposals.

17 CHAIRMAN SANTANA: I want to also make a
18 comment regarding the second issue, which is that,
19 once you have established this commonality in terms of
20 the disease and the biology, then what additional
21 information would you want to legally support a
22 product claim for children with cancer? My position

1 would be that, if the agent that you are discussing,
2 that you are targeting, is a biologic with the common
3 pathway, and that indication exists also in children,
4 that you would have the same requirement, that you
5 would require a Phase III study that would indicate
6 the impact of that, wouldn't you?

7 DR. HIRSCHFELD: Not necessarily. We have
8 been exploring broadly in pediatrics the issue of
9 extrapolating efficacy findings. I think the paradigm
10 that Dr. Adamson was discussing is something which
11 might be acceptable. I don't think there would be a
12 regulatory requirement to repeat an efficacy study
13 with the definition -- and I'm looking at our
14 colleagues over in that corner -- that an efficacy
15 study is a study which is designed to establish the
16 efficacy rather than just demonstrate an
17 exposure/response relationship. I think the
18 exposure/response relationship could be sufficient,
19 but I will ask Dr. Pazdur.

20 DR. PAZDUR: Yes, I think I would agree
21 with Steve. Let's take a specific example. If we
22 were dealing with Hodgkin's Disease and somebody did

1 a randomized study and proved the efficacy and
2 combination of a drug and proved what we would be
3 looking for, probably a survival advantage or a
4 curability clinical benefit, probably since the
5 disease would be quite similar in a child, the
6 childhood population -- and correct me if I am wrong
7 since I am not a pediatric pediatrician -- but if that
8 was a similar disease, we probably would accept Phase
9 II data, since it probably would be very difficult to
10 do and replicate a Phase III trial in that identical
11 population.

12 Here, again, it really depends on how
13 comfortable we are that these are exactly the same
14 diseases, but we don't want to be overregulatory or
15 overburdensome in this regard. I think there could be
16 a kind of bridging that could occur with Phase II data
17 here, again, emphasizing the safety that you
18 previously mentioned for a pediatric population and
19 look at a surrogate end-point such as response rate
20 toward a particular disease, and making sure the
21 duration of that response was meaningful.

22 CHAIRMAN SANTANA: Thanks for a

1 clarification.

2 Other comments or questions? Jerry?

3 DR. FINKLESTEIN: This question is either
4 to Rich or to Steve. At the last meeting we spent a
5 lot of time in comparing adult and pediatric tumors.
6 In fact, we made the comment maybe histology was on
7 the way up because molecular biology was on the way
8 in.

9 My question is whether the incentive
10 program would apply to those pharmaceutical companies
11 that would like to use molecular biology as a way of
12 studying pediatric tumors. Using your example of
13 prostate cancer, for example, with some signal, could
14 that be invoked and would you accept that? So I am
15 asking it, actually, from an industrial point of view.

16 DR. HIRSCHFELD: The incentive program
17 doesn't require any relationship between the adult
18 tumor and a pediatric disease. In fact, within the
19 FDA in general we have adult indications which were
20 approved in one Division, in one disease area, and the
21 pediatric indication that is being studied is in a
22 completely different area. So there's no need for a

1 biological or mechanistic linkage in any way.

2 However, if the rule is invoked, that does
3 not preclude qualifying for the exclusivity extension.
4 That would then require further discussion. It is not
5 an automatic trigger or something that one can assume.
6 It would require specific discussion, but that's
7 plausible.

8 DR. PAZDUR: I think it is also important
9 to put in context the rule as it can be applied. What
10 we are dealing here, from our previous meetings, is a
11 relatively limited number of diseases that really go
12 back and forth. You could talk about acute leukemias,
13 for example, some lymphomas, some brain tumors.

14 But, remember, the sponsor has to be
15 studying the drug in that indication in the adult
16 population, and really when you take a look at what
17 indications are being studied in adult populations,
18 for example, they are the big diseases. They are
19 breast cancer. They are colon cancer, prostate
20 cancer, pancreatic cancer. We have very few
21 applications where the rule really can be nailed down,
22 where we could have this linkage between and exert our

1 regulatory authority in that regard. So I think we
2 have to put this in some context of the real world,
3 and that is why, as Steve already mentioned, the
4 exclusivity arrangements probably have a greater
5 degree of flexibility really to encourage drug
6 development in pediatrics.

7 CHAIRMAN SANTANA: Dr. Boyett?

8 DR. BOYETT: Just a point of
9 clarification: Suppose you take your Hodgkin's
10 Disease example and you've got efficacy data in adult
11 and you do a Phase II trial and you show some response
12 in pediatric Hodgkin's Disease. So now you grant a
13 labeling indication in pediatrics.

14 You know, there are very few pediatric
15 cancers that are cured by single agents. How to
16 incorporate one of those single agents into a regimen,
17 that's a different question. If you grant this
18 labeling, what is going to be the implication of COG,
19 for instance, trying to learn how to use this
20 particular drug in a regimen to treat newly-diagnosed
21 Hodgkin's Disease patients?

22 DR. HIRSCHFELD: Our history of approvals

1 is actually that very often in the label the product
2 that is being granted the claim is being granted the
3 claim as part of a regimen. A recent example is the
4 approval of Irinotecan, where it isn't Irinotecan that
5 is approved; it is Irinotecan in the use with
6 combination with other drugs in a particular setting.

7 So in the case where a new Hodgkin's
8 therapy would come along, boy, if we had something
9 that is as a single agent could treat the disease,
10 that would be fairly spectacular, and it would warrant
11 that. But, in general, the data that are being
12 submitted are data where it is not for monotherapy but
13 as part of what, hopefully, is a therapeutic advance
14 over previous regimens.

15 Rick, do you want to comment?

16 DR. PAZDUR: Yes, because probably what we
17 would do in the adult indication, it probably would be
18 used in combination with other drugs, and that same
19 combination would be studied in the pediatric
20 population, looking for similar response rates between
21 the adult population and the pediatric population.
22 Here, again, it is a bridging aspect. We wouldn't

1 just take a single agent and say, well, you have 20
2 percent response rate and, therefore, have activity in
3 Hodgkin's Disease and say, well, that's sufficient for
4 approval in --

5 DR. BOYETT: I guess I was misinterpreting
6 the use of Phase II here because your intent in --

7 DR. PAZDUR: Let me clarify that.

8 DR. BOYETT: Yes.

9 DR. PAZDUR: Probably a more accurate
10 description would be a single-arm trial looking for
11 response rate.

12 DR. HIRSCHFELD: An exposure/response
13 study is what we usually use in broader pediatric
14 term, not Phase II in the narrow sense.

15 CHAIRMAN SANTANA: Dr. Korn, one last
16 comment on this issue, please.

17 DR. KORN: Well, that's going to be kind
18 of tough now, isn't it? So you're going to have a
19 combination therapy, a small Phase II trial, and you
20 are going to try to show that response rate, whatever,
21 is consistent with the small Phase II adult study. I
22 mean, I'm not sure what that means. You almost can

1 say, well, why bother, because you're not going to
2 find anything out from doing that anyway?

3 DR. PAZDUR: Well, here, again, I think
4 there is some elements of safety that we would
5 consider by looking at it in a Phase II study, which
6 I think is important, as Victor implicated. Remember,
7 these diseases -- and here, again, the link of how
8 comfortable we feel between the disease and the child
9 and in the adult is one that is really going to
10 mitigate what degree of information that we would want
11 from the sponsor and the clinical trial. If we really
12 believed that these were identical diseases, to make
13 a sponsor do a separate Phase III study with a
14 combination against the standard therapy of "X"
15 hundreds of patients may not be warranted here to show
16 either superiority or non-inferiority.

17 DR. KORN: Right. Well, the alternative
18 is not to do the Phase II study, but do a small safety
19 study then.

20 DR. PAZDUR: Here, again, the Hodgkin's
21 disease might not be the best example. It is an
22 example that I threw out, but, here again, a lot of

1 these factors are mitigated by how comfortable the
2 feeling is and the scientific underpinning between
3 extrapolations.

4 DR. HIRSCHFELD: I would just add to that
5 that I think we're ethically bound to do the studies
6 only in patients with the diagnosis. If we did even
7 some modest study and saw no responses, I think
8 everyone would begin to get worried. So although the
9 purpose of the study wouldn't be to establish
10 efficacy, you would certainly want to make note or
11 want to be reassured that you were getting the same
12 type of response.

13 DR. KORN: Right, but I can understand for
14 mono-therapy but for combination therapy, you are
15 going to get responses. So that's not going to really
16 be an issue.

17 CHAIRMAN SANTANA: That would be the added
18 value.

19 Okay, let's move on because I think we
20 have covered this one pretty much.

21 So the third question is relevant to mono-
22 therapy versus combination therapy. That is, "If a

1 therapy is intended to be used as part of a
2 combination, are monotherapy studies in children
3 advisable? If so, what types of studies should be
4 implemented prior to initiating the combination
5 studies?"

6 Peter?

7 DR. ADAMSON: I'll just comment. We are
8 more limited in pediatrics than we are in adults in
9 this situation. If a single agent has no prospect for
10 direct benefit, and is greater than minimal risk, we
11 cannot perform a single-agent study, I think. At
12 least that would be my interpretation of the
13 regulations.

14 However, I think -- and I kind of shudder
15 to have used the word "window" here, but I think one
16 can consider a single-agent window, and let me expand
17 what I mean by that. Where one starts with a new
18 agent, determines acute toxicity, defines some
19 pharmacokinetics, and continues with a combination,
20 and I have a couple of examples that I will share with
21 you, which is where we have taken this approach.

22 The first is a study that Frank Balis and

1 Kathy Warren led with RMP-7 and carboplatin, and the
2 subsequent one will be a study that COG will be
3 starting soon with the antisense compound Genasense.
4 So RMP-7 is a drug that modulates the blood/brain
5 barrier. There was a fair amount of pre-clinical data
6 and some adult data that it could potentially increase
7 the efficacy of standard cytotoxic agents, but by
8 itself RMP-7 was not known to have any anti-cancer
9 potential.

10 So the pediatric trial design was the
11 following: The first day of the first cycle of
12 therapy, the patient received Cereport as a single
13 agent to determine its acute toxicity, its acute
14 tolerability, as well as the pharmacokinetics. Then
15 it was immediately followed in day two and day three
16 of the first cycle by the combination of carboplatin
17 and Cereport, Cereport being administered at the time
18 of peak carboplatin exposure.

19 All subsequent cycles were then two-day
20 exposures of just the combination of the two. So in
21 this case we know we were not getting data as far as
22 any chronic toxicity of single-agent Cereport. This

1 is a drug, however, that essentially only has acute
2 toxicities, but we were getting a fair amount of
3 information at the same as allowing patients a full
4 benefit in a given cycle of being exposed to an active
5 combination.

6 Similarly with Genasense, which is a BCL2
7 antisense compound, the trial design that we are
8 proposing, and that CTAP will soon review, is that
9 there is a lot of data, first of all, that to get
10 maximal decrease in BCL2 expression, you need a
11 sustained exposure to the antisense compound. So
12 there will be a seven-day continuous infusion study of
13 the antisense compound, and during the initial four
14 days the patient is only going to be exposed to the
15 antisense compound as a single agent.

16 We will get some acute toxicity
17 information here. We will get some pharmacokinetic
18 data here, and then during that first cycle they will
19 then get exposed to the combination of some standard
20 cytotoxic agents, in this case doxyrubicin and
21 cyclophosphamide, in conjunction with the agent that
22 by itself would have minimal activity as a single

1 agent.

2 So we have addressed this in pediatrics,
3 and we have done it in situations where it has been,
4 I think, relatively straightforward to do, and that is
5 when we are either anticipating only acute toxicities
6 or when the biology of the drug action warrants
7 administration of the drug prior to combination.

8 However, during a trial where there is
9 just a cycle of drug with no potential for therapeutic
10 benefit, I do not think it is going to be feasible in
11 pediatric patients.

12 CHAIRMAN SANTANA: Yes, I want to expand
13 on that. I think that the intent defines the study
14 that you want. So if we know pre-clinically or from
15 some other data that the agent by itself doesn't play
16 a major role, I think it would be both scientifically
17 and ethically invalid to do a single-agent trial if
18 ultimately that is going to be needed to be done in
19 combination.

20 So I think one has to be very specific
21 about the agent that one is talking about, and what
22 one knows about that agent a priori before one

1 mandates that that agent be studied as a single agent,
2 based on the intent.

3 DR. PAZDUR: How does one know actually
4 that, that the agent has no activity? You know, here
5 again, there is activity and activity; one could be
6 activity measured as response rate for a cytotoxic
7 drug versus time-to-progression for a more cytostatic
8 therapy, and just to say, well, because the drug does
9 not produce response rate, one does not have to
10 demonstrate single-agent activity would be somewhat
11 hard necessarily to swallow for us.

12 CHAIRMAN SANTANA: No, I agree with you.
13 I think with cytostatics, it is very controversial and
14 it is very difficult. With cytotoxics, I think it is
15 a little bit easier in terms of answering the
16 question. With cytostatics, you are faced with the
17 issue that you really may not know if by a single
18 agent given over a prolonged period of time you do get
19 some activity.

20 So I think in that scenario you are really
21 going to have to rely very heavily on some pre-
22 clinical data and what data you may discern from adult

1 studies before you mandate a single-agent pediatric
2 study.

3 Frank?

4 DR. BALIS: The area this most applies to
5 is modulating agents, agents that modulate resistance,
6 for example, to anti-cancer agents, where giving them
7 alone obviously makes no sense.

8 But the other, the converse is also true.
9 There are a number of studies with MBR inhibitors in
10 adults where the agent, the chemotherapy agent, was
11 given alone, and then on a second cycle it was given
12 with a modulating agent.

13 I think I have the same difficulty doing
14 that type of trial in pediatrics, in that many of the
15 diseases that we treat tend to progress very rapidly
16 if not given effective therapy. So even doing a
17 chemotherapy alone followed by a cycle later with
18 modulating agents I think is a difficult trial design
19 to undertake in our population, if there has been
20 efficacy shown for that modulating agent in adults.

21 CHAIRMAN SANTANA: Any other comments or
22 advice on this issue?

1 (No response.)

2 CHAIRMAN SANTANA: Okay, so let's move to
3 the fourth question which is the Phase II window
4 design. For the sake of time, I won't read the
5 paragraph, but I think the question is: "What
6 circumstances (for example, types of diseases,
7 expected results with available therapy, prognosis,
8 types of patients) would warrant a Phase II window
9 design?" And I'll let Peter comment on that, and then
10 I will give my insight, too.

11 DR. ADAMSON: I think I made my opinion
12 known. So, in fact, I don't even have a slide on this
13 one, but I would echo what Malcom had said earlier.
14 I think in order to accelerate the drug development
15 process, we need to start believing our own data. In
16 the relapse setting for that vast majority of
17 childhood cancer, not all but the vast majority,
18 including high-risk ALL, we, in general, don't have
19 meaningful salvage therapy coming off of current
20 frontline protocol.

21 I think a Phase II window study that
22 either a modulating agent or, in fact, a novel agent

1 in certain circumstances may be more appropriate in
2 the relapse setting than it is going to be in the
3 upfront setting for diseases where there is no known
4 effective standard therapy, and I would probably limit
5 that to brainstem glioma at this point. It may be
6 acceptable to do it there. However, beyond that, I
7 think we run into many of the ethical issues that have
8 been discussed, as well as the value of doing them
9 that I had mentioned earlier.

10 CHAIRMAN SANTANA: Yes, my comment was
11 going to be, as you heard earlier, that I think the
12 consensus document from four or five years ago has
13 been a good tool and a good guideline for answering
14 this question. Until that document is revisited, I
15 think that document should serve the basis to answer
16 this question.

17 So for those of you who haven't read it,
18 I would encourage you to read it because I think it
19 does provide some insight into the potential type of
20 patients, the expected results, and some of the
21 relevant issues regarding the ethics of these trials.
22 So until we revisit that guideline and that consensus,

1 I think that serves as a good parameter for us to
2 answer this question to give advice to the FDA.

3 Frank?

4 DR. BALIS: Yes, I think we are moving
5 into targeted therapy. The one potential area where
6 it could be useful is if we want to define a
7 biological effect of a drug that has a specific target
8 that is completely separate from any effect that
9 standard therapy has on a tumor, because so many of
10 our tumors now are treated neoadjuvantly, and we have
11 the opportunity potentially to get tumor tissue,
12 because we are doing a clinically-indicated procedure
13 in those patients at some point later during their
14 therapy that we could administer drug maybe even in
15 combination with standard therapy during the
16 neoadjuvant phase, where we could measure a biologic
17 effect when we go in and actually remove their tumor.

18 DR. BERNSTEIN: I think that Peter is a
19 little overly restrictive about disease categories.
20 I think there are a variety of sarcomas, metastatic at
21 diagnosis, for instance, where the prognosis is
22 sufficiently poor so that one could consider the

1 addition of new agents early on rather than waiting
2 for recurrence.

3 I won't push the point too hard because I
4 actually think that, for the immediate question, which
5 is, how are we going to give guidance to the FDA, I
6 think that there will be rare circumstances in which
7 window trials are actually going to be very
8 informative in terms of the things that you're looking
9 for.

10 I agree with what Victor said, that I
11 think the document that was produced by our consensus
12 meeting, which with Susan I had the privilege of
13 attending several years ago, I think is reasonable as
14 a guidance.

15 CHAIRMAN SANTANA: Do you want to make
16 some final comments and then, Wayne, because I think
17 we are running short on time?

18 DR. ADAMSON: Yes, I am going to turn this
19 over to Wayne. The only one I want to talk about, and
20 I am going to jump to that, is on prioritization.

21 The challenge for us is that we simply
22 cannot study all the drugs that are in the

1 developmental pipeline in children. So we have a
2 choice. We can do it randomly or we can look at pre-
3 clinical models that we know in most cases have not
4 yet been validated, but at least may give us some
5 basis for helping to prioritize.

6 What I find is a remarkable situation now
7 -- and, again, this may be a little bit overstated,
8 but with FDAMA in the final rule, we are faced with a
9 situation whereby it may be easier to administer a new
10 drug to a child with cancer than it will be to
11 administer the new drug to a mouse. I say that
12 because intellectual property issues now -- and this
13 is a two-way street; this is not just industry; this
14 is academia working with industry, and basically
15 lawyers going at it with lawyers -- where we have no
16 pre-clinical data in pediatric tumors at a time when
17 we are ready to embark on pediatric studies.

18 This is a situation that we are going to
19 have to address, and we are going to have to improve
20 upon because the problem is just going to expand as
21 the number of agents in the pipeline increase. Until
22 we solve the issue of overcoming the intellectual

1 property debate, where we can get new agents into
2 models that we openly will say have not yet been
3 validated, but which we intend to validate over time,
4 we are going to be operating in the blind as far as
5 being able to prioritize.

6 That is simply stated here, that I think
7 pre-clinical models for pediatrics, we are likely to
8 have to rely on more heavily than one will have to do
9 it in the adult situation.

10 So let me turn it over to Wayne, who I
11 think is --

12 DR. RACKOFF: In the interest of time, I
13 will just do it from here because I've only got three
14 or four slides, and I'll provide them, if you want,
15 but they are fairly straightforward and really address
16 the last two points.

17 I just want to warn people that the last
18 Advisory Committee I took part in was in 1977, the
19 National Health Insurance Advisory Committee. I was
20 a staff member, and you know how successful that was.
21 So I hope this project will be a little more
22 successful in coming up with specific guidelines.

1 I am speaking now, it is not the opinion
2 of Johnson & Johnson; it is not the opinion of any one
3 group. Raj Malik and I, who chair the COG Committee,
4 have conferred a little bit during the breaks. What
5 I would like to do is provide in five minutes not an
6 industry opinion, but a perspective on what's gone on
7 actually in the last four meetings.

8 I think that the overall goal here is a
9 little different from what's stated in the law. It's
10 been there in the air in all the meetings. The goals
11 are early access to new agents, to accelerating the
12 process of drug development for new agents, and,
13 finally -- and this is the industry perspective -- in
14 trying to get some consistency in that process.

15 Now I think there are three things that
16 have to be taken into account that have come out at
17 these meetings. One is that pediatric rule and
18 exclusivity, although we have tried to divide them for
19 these meetings, I'm a "lumper" and that's why I like
20 these meetings, because the rule lumps adult and
21 pediatric cancers together. I think the Pediatric
22 Rule and exclusivity have to be considered in toto as

1 moving toward that goal, much in the same way as the
2 Bill of Rights, the Civil Rights Act, and Voting
3 Rights act are not standing alone doing what they are
4 supposed to do.

5 So I think that as the Agency moves
6 forward, our advice, my advice is that we consider
7 these things working in concert, and that's where
8 Peter established a gap, but I think, again, that
9 pediatric exclusivity and the way these guidances are
10 written around pediatric rule can help to fill that
11 gap.

12 Second, and I agree with Peter and I think
13 it's the major issue that we face in pediatric drug
14 development in cancer, is that the patient-to-agent
15 ratio is going down, not going up, because I think
16 Pediatric Rule and pediatric exclusivity have been
17 effective. There is anticipatory action being taken
18 by a number of companies. Here I will speak about my
19 company where there's a Vice President for Pediatric
20 Drug Development and a whole Pediatric Drug
21 Development Group.

22 But we are dealing with small populations,

1 and Rick Pazdur alluded to this. Where the Pediatric
2 Rule is applied, it's always going to be applied in
3 small adult populations and small pediatric
4 populations because those cancers, with very few
5 exceptions that are linked in the Pediatric Rule
6 specifications, are small tumor burdens, public health
7 burdens.

8 So we need to link, but we need to link
9 for the sake of the adults who have AML and for the
10 sake of the children who have AML. I think there are
11 two ways to link. They have come out at these
12 meetings. One is sequential development, and I think
13 there are advantages to that. What needs to be
14 stated, I think, in the guidances are what allowances
15 will be made for prior probabilities, not necessarily
16 using a Bayesian approach or a classical approach, but
17 what allowances will be made in the development
18 process for prior knowledge. I think to the extent
19 that those can be specified clearly, they will
20 encourage further anticipatory development without
21 invocation of the rule.

22 Second is there's parallel development,

1 and a lot of people, I think, on the academic side and
2 in COG would like to see us do parallel development.
3 In parallel development you'll get faster development,
4 too, but then you need allowances for combining data
5 in studies run in parallel or linking the studies
6 themselves. Here I think the COG and the NCI come
7 into play more than the Agency.

8 That brings to one of the other points,
9 which is that, in setting priorities, we have to have
10 COG, NCI, CTAP, the Agency, and industry at the same
11 table. Now the industry people can't be at the same
12 table at the same time because there are intellectual
13 property issues. But I think that there has to be
14 some sense in the guidances that provides a fair and
15 consistent way to combine all four of those forces to
16 be able to set priorities, because that's the only way
17 we're going to deal with this patient/agent ratio
18 being very low.

19 So, with regard to specific invocation of
20 the rule, and this is the final set of points, I think
21 that the guidances should set out, or the letters, or
22 at the meetings, that go out after the meetings, what

1 bridging studies are required, what specific bridging
2 studies will be acceptable, to the extent that the
3 Agency can do that within the law, and, finally, what
4 will be a significant treatment advance is going to be
5 a very important point in setting priorities.

6 To the extent possible, if the guidance
7 that comes out of these meetings can set out what is
8 significant treatment advance, I think that that will
9 help, again, determine how much anticipatory activity
10 there will be on the part of the industry drug
11 developers.

12 So, in summary, again, I think the rule
13 and exclusivity are working. So I think to the extent
14 that these guidances build on that, they are going to
15 be very important. I think that the major issue from
16 both the company's standpoint and I think from COG and
17 every other standpoint is that patient numbers are
18 limited, and we have to have specific guidances that
19 will combine the forces of NCI, COG, industry,
20 interested members, and the Agency, to set priorities
21 in a way that makes sense and that is consistent and
22 fair to both industry and to patients.

1 CHAIRMAN SANTANA: Thank you for those
2 comments, Wayne. As you note, there is that effort
3 underway. There is a group that meets at COG that has
4 representatives from FDA and industry that tries to
5 address some of these issues. I think there's still
6 a lot more work to be done.

7 DR. RACKOFF: One more point that came up,
8 if you don't mind, real quickly: There is work going
9 on, too, on this issue of material transfer for pre-
10 clinical studies. It is going to take some time and
11 it is going to take some battles among lawyers sitting
12 down in a room, locking them up, to come up with what
13 might be a master agreement that's acceptable, but
14 under Malcom's guidance that effort is underway.

15 CHAIRMAN SANTANA: I want to thank you for
16 those comments, Wayne.

17 Dr. Hirschfeld?

18 DR. HIRSCHFELD: I also want to thank Dr.
19 Rackoff for his participation previously as an
20 observer and now at the table with us. We hope that
21 we can continue to have industry representatives on
22 the table for this Committee forever essentially.

1 We will also, I think, have to acknowledge
2 that, of the products that are available to treat
3 patients with cancer, whether they are children or
4 adults, it's been the pharmaceutical industry that has
5 done the brunt of development work and has taken the
6 risks and the distributions and maintained the quality
7 control, and I think should be acknowledge for the
8 contributions that are made in that regard to the
9 public health.

10 I wanted to pick up on the theme of the
11 matrix because we all feel we are part of a matrix.
12 We should in no sense be perceived as adversarial or
13 that one has a barrier to overcome, or if we can only
14 get around the regulatory hurdles, but rather that we
15 view the regulatory mechanism as a way to ensure high-
16 quality products for patients, ethical and consistent
17 scientific development.

18 We have been working ourselves with
19 international colleagues, and I think both the
20 pharmaceutical industry and the regulatory community
21 have started on a path which I hope there's no return
22 from. That is to get greater international

1 cooperation, and it is through international
2 cooperation I think that we can address some of these
3 issues of limitations of numbers and prioritization.
4 I am very heartened that we have at this meeting some
5 international representation and that we look for
6 further development in this arena as well.

7 CHAIRMAN SANTANA: I want to echo that.
8 I think it has to be a conversation that includes many
9 different parties. I was encouraged to see that there
10 were colleagues from across the ocean who came today
11 and provided some of their effort and time at this
12 meeting. So I want to personally and publicly thank
13 you for that effort.

14 DR. PAZDUR: But I think it's important
15 that we realize that drug development, in essence, is
16 an international, global development process that
17 occurs. So we don't approve drugs in the United
18 States in isolation. In fact, our regulatory actions
19 have great implications not only in Europe, but
20 throughout South America and Asia.

21 CHAIRMAN SANTANA: That is correct.

22 DR. PAZDUR: Just to echo Steve's words,

1 it is basically we have to be cognizant of our more
2 widespread regulatory activities.

3 Nevertheless, getting back to this idea of
4 how do we prioritize drugs, I think this is one of the
5 things that we will be using this group as in future
6 areas, to give us the scientific information both
7 using the Pediatric ODAC Subcommittee as well as
8 individual members, in consultation with us on
9 individual applications.

10 There obviously are many drugs. Which
11 ones to study in pediatrics needs to be really
12 addressed by the people that are studying them and
13 treating the patients. Not all drugs are appropriate,
14 obviously, to be studied in a pediatric population,
15 and we need to have that conversation with you on a
16 long-term basis.

17 CHAIRMAN SANTANA: And we look forward to
18 providing whatever help and guidance we can to the
19 Agency in that regard.

20 If there are no further comments, I want
21 to thank -- I'm sorry. I'm sorry, go ahead, Susan.

22 DR. WEINER: I thought that today's

1 meeting was really a very good one, Steve, and I
2 thought that the discussion was authentic. I very
3 much appreciate the notion of the matrix, that is, of
4 all participants, since we have an important charge.

5 But I guess what I would like to add is
6 that I think that at every step of the way we have to
7 be cognizant, every component of this matrix has to be
8 cognizant of how to cut corners, how to make the
9 process more efficient, where things can be more
10 consistent, and how to promote appropriate uniformity.
11 There are certain variables in this process which we
12 can control -- sample sizes, ethics, et cetera. Where
13 we can control it, I think it's really an obligation
14 to the kids and families. Thank you.

15 CHAIRMAN SANTANA: Thank you, Susan.

16 I think we have fulfilled our goals as
17 best we could, Dr. Hirschfeld and Dr. Puzdur. So,
18 with no further comment, I want to thank everybody and
19 declare this meeting closed. Thank you.

20 DR. HIRSCHFELD: Thank you.

21 (Whereupon, the proceedings concluded at
22 4:50 p.m.)

C E R T I F I C A T E

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This is to certify that the foregoing transcript
in the matter of: MEETING

Before: FOOD AND DRUG ADMINISTRATION
ONCOLOGIC DRUGS ADVISORY COMMITTEE
PEDIATRIC SUBCOMMITTEE

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